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(54) Treatment of skin disorders.

(57) A topical composition for skin treatment contains an anti-inflammatory glucocorticoid in combination with an essential fatty acid (EFA) of the n-6 or n-3 series or equivalent poly-unsaturated fatty acid, as such or in the form of a physiologically acceptable derivative convertible in the body thereto.

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TREATMENT OF SKIN DISORDERS

FIELD OF INVENTION

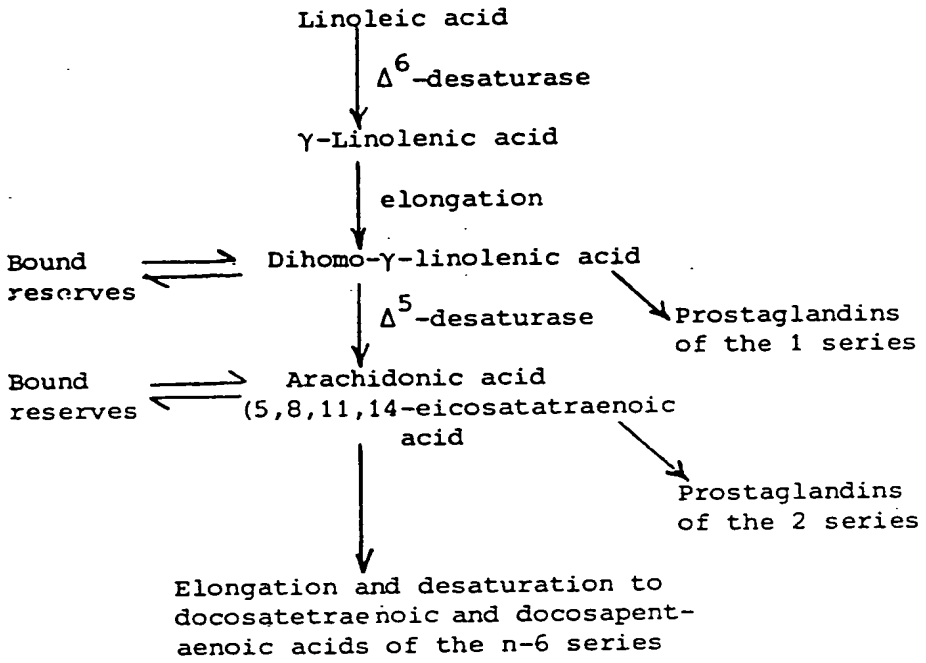
The invention relates to compositions of γ-linolenic acid and related materials with anti-inflammatory glucocorticoids and to the treatment of inflammatory skin disorders with them.

BACKGROUND AND EXPLANATION OF INVENTION

Much interest has been shown in recent years in essential fatty acid metabolism, especially in its relation to prostaglandin (PG) metabolism and in particular to the balance of 1-series and 2-series PGs in the body.

The main dietary essential fatty acid (EFA) utilised in the fully healthy human body is linoleic acid, but the Δ^6-desaturase that converts it to the next acid in the n-6 series, namely γ-linoleic acid (GLA) is at a low level of activity in many conditions. The giving of γ-linolenic acid is beneficial in such conditions and has been the subject of earlier patent applications of the present inventor which discuss the essential fatty acids and their relation to PG metabolism.

Specifically, prostaglandin precursors include linoleic acid, γ-linolenic acid and dihomo-γ-linolenic acid (DGLA), conversion in the body being as follows:



SKIN CONDITIONS

Many inflammatory skin conditions are associated with excess formation of prostaglandins and cyclo-oxygenase and lipoxygenase products from arachidonic acid. It is generally believed that glucocorticoid ointments and the like are successful in these conditions because (apparently by inhibition of phospholipases concerned) they block the release of arachidonic acid from phospholipid and other bound precursors or reserves. They have a similar effect on DGLA release. Thus glucocorticoid treatment leads to a situation in which both DGLA and arachidonic acid fail to give rise to their metabolites because they are not released from store.

This effect of blocking EFA release from stores the

inventor believes desirable with regard to arachidonic acid (of which bodily reserves are large) and probably to explain the therapeutic effects. On the other hand, both free EFAs and PGs and other EFA metabolites play important roles in the skin and their absence is believed to explain some of the undesirable side effects of long term topical steroid treatment such as skin atrophy. The 1-series PGs in particular have desirable actions and the inventor has seen that if the steroid action in blocking formation of all PGs and other products can be balanced by selective restoration of 1-series PG formation, a desirable therapeutic result will occur, especially in long term use. This situation is achieved by combining a glucocorticoid ointment or other preparation with a precursor of 1-series PGs such as linoleic acid, GLA or DGLA. These fatty acids lead to an increase in the 1-series PG precursor, DGLA, in a form which can be converted to PGE1 even in the presence of glucocorticoids.

Of the three fatty acids, GLA is the most desirable because unlike DGLA it has other effects on the skin which do not seem to depend on its conversion to PGs. GLA and linoleic acid, but not DGLA, can for example, restore normal skin permeability to water in animals deficient in essential fatty acids. Of the two, GLA is preferable to linoleic acid because of the many factors known to inhibit the Δ^6-desaturase. Little of the GLA is converted through to arachidonic acid because the level of Δ^5-desaturase activity is low in humans and also because of

a further effect of glucocorticoids which is believed important, namely that they have been reported actually to inhibit the Δ^5-desaturase (De Gomez Dumm et al, J. Lipid. Res. 20: 834-9, 1979). They would thus increase the ratio of DGLA and its products to arachidonic acid and its products. Since the products derived from arachidonic acid appear to be considerably more pro-inflammatory than those formed from DGLA, such enzyme inhibition contributes to the anti-inflammatory effect.

OTHER FATTY ACIDS

Emphasis above is on the relation of EFAs to prostaglandins. However, as noted, both the EFAs themselves and their biological cyclo-oxygenase and lipoxygenase products have independent functions in the skin. The effect of EFAs as such is well illustrated by the unusual 18:3 fatty acid, columbinic acid (n-6,9,13 trans) which cannot be converted to prostaglandins (Houtsmuller, Progr. Lipid. Res. 20: 889-96, 1982). This fatty acid is able to correct most of the skin consequences of EFA deficiency, illustrating that the fatty acids themselves have key roles in the skin. Columbinic acid is found in abundance in the seeds of Aquilegia vulgaris.

Another group of fatty acids whose function in the skin is uncertain but which are believed to have a role since they are present in significant quantities is the n-3 series of EFAs derived from α-linolenic acid.

Glucocorticoid inhibition of phospholipase enzymes is

to be expected to limit the availability of the n-3 acids to the skin also. They are set out with the relation of their conversion pathway to that of the n-6 EFAs in the following table:

n-6		n-3	
18:2	$\Delta^{9,12}$ (linoleic acid)	18:3	$\Delta^{9,12,15}$ (α-linolenic acid)
↓	Δ^{6} desaturase	↓	
18:3	$\Delta^{6,9,12}$ (γ-linolenic acid)	18:4	$\Delta^{6,9,12,15}$
↓	elongation	↓	
20:3	$\Delta^{8,11,14}$ (dihomo-γ-linolenic acid)	20:4	$\Delta^{8,11,14,17}$
↓	Δ^{5} desaturase	↓	
20:4	$\Delta^{5,8,11,14}$ (arachidonic acid)	20:5	$\Delta^{5,8,11,14,17}$
↓	elongation	↓	
22:4	$\Delta^{7,10,13,16}$ (adrenic acid)	22:5	$\Delta^{7,10,13,16,19}$
↓	Δ^{4} desaturase	↓	
22:5	$\Delta^{4,7,10,13,16}$	22:6	$\Delta^{4,7,10,13,16,19}$

The pathways are not normally reversible nor, in man, are n-3 and n-6 series acids interconvertible.

The acids, which naturally are of the all-cis configuration, are systematically named as derivatives of the corresponding octadecanoic, eicosanoic or docosanoic acids e.g. $\Delta^{9,12}$-octadecadienoic acid or $\Delta^{4,7,10,13,16,19}$docosahexaenoic acid, but numerical designation such as, correspondingly, 18:2 n-6 or 22:6 n-3 is convenient. Initials, for example, DHA for 22:6 n-3 (docosahexaenoic acid), are also used but do not serve when

n-3 and n-6 acids of the same chain length and degree of unsaturation exist. Trivial names in more or less common use in the n-6 series are as shown. Of the n-3 series only 18:3 n-3 has a commonly used trivial name, α-linolenic acid. It was characterised earlier than γ-linolenic acid and reference in the literature simply to linolenic acid, especially in the earlier literature is to the α-acid.

In further regard to the significance of the n-3 series acids it may be noted that as between the n-6 and n-3 acids the elongation reactions (e.g. GLA to DGLA) are highly efficient and there is very little competition either way. In contrast, the two series of fatty acids are in competition in the desaturation processes. The n-3 fatty acids interfere with both Δ^6 and Δ^5 desaturation in the n-6 series. This competition seems to occur even when the n-3 fatty acid is not actually a substrate for the enzyme concerned. For example, 20:5 n-3 competitively inhibits the Δ^6 desaturation forming GLA from linoleic acid and overall the presence of n-3 fatty acids in a combination leads to some inhibition of the conversion of DGLA to arachidonic acid by the Δ^5 desaturase. As a result of the presence of n-3 EFAs, the efficiency of either GLA or DGLA in increasing the ratio of DGLA products (1-series PGs) to arachidonic acid products (2-series PGs) will therefore be increased so that compositions in which n-3 acids accompany GLA or DGLA are of particular value.

THE INVENTION

In the light of the above it will be seen that at its broadest the invention is to use anti-inflammatory glucocorticoids in combination, for their effect on the skin, with one or more EFAs of the n-6 or n-3 series (preferably other than arachidonic acid because of its potential action in increasing 2-series PG synthesis) or equivalent polyunsaturated fatty acids, in their effects on the skin, of which columbinic acid is an example. Preferably, for the specific effect on PG balance, the acids are the earlier n-6 EFAs linoleic acid, GLA and DGLA of which for the reasons explained GLA and DGLA are preferred and GLA is best.

Anti-inflammatory glucocorticoids are a well recognised class of natural or synthetic steroids having biological effects similar to naturally occuring hydrocortisone (cortisol) and are fully described in, for example, Martindale's Extra Pharmacopeia, 27th Edition, 1977, pages 389-440 or in Goodman and Gilman, Pharmacological Basis of Therapeutics, 6th Edition, pp 1470-1492, 1980, to which reference may be made. Examples include hydrocortisone itself, cortisone, betamethasone, dexamethasone, fluprednisolone, methylprednisolone, paramethasone, prednisone, prednisolone, triamcinolone, beclomethasone, clobetasol, cloprednol, cortivazol, deoxycortone, desonide, desoxymethasone, diflucortolone, fluclorolone, fludrocortisone, flumethasone, flunisolide, fluocinolo: fluocinonide, fluocortolone, fluoromethalone, fluperolone, fluprednid flurandrenolone, formocortal, halcinonide, hydrocortamate, medrysone methylprednisone, paramethasone, prednisolamate and prednylidene. Concentration ranges are suitably, by weight, 0.01 to 30% fatty acid, 0.01 to 10% steroid in a topical application base.

The invention also extends to use of such compositions in, and the preparation of such compositions for, treating inflammatory skin

disorders or enhancing the effect of anti-inflammatory glucocorticoids on the skin, examples of the disorders being contact dermatitis, atopic dermatitis, psoriasis, and seborrhoeic dermatitis.

FORMS OF ESSENTIAL FATTY ACID

The acids may be used as such or in any physiologically compatible form equivalent to them, for example, those referred to for γ-linolenic acid below and general reference to the acids herein, including in the claims, is to be taken as including such derivatives. Equivalence is demonstrated by entering into the pathways quoted herein as evidenced by effects corresponding to those of the acids themselves or their natural glyceride esters. Thus, indirect identification of useful derivatives is by their having the valuable effect in the body of the acid itself, but conversion can be shown directly by gas chromatographic analysis of concentrations in blood, body fat, or other tissue by standard techniques, for example those of Pelick et al page 23, "Analysis of Lipids and Lipoproteins" Ed. Perkins, American Oil Chemists Society, Champaign, Illinois, U.S.A.

In outline the method is suitably that plasma samples (1 ml) are extracted with chloroform:methanol (2:1). The extract is filtered through sodium sulphate, evaporated to dryness, and taken up in 0.5 ml chloroform:methanol. The lipid fractions are separated by thin layer chromatography on silica gel plates. The phospholipid fraction, taken to reflect essential fatty acid contents most sensitively, is methylated using boron trifluoride-methanol. The resulting methyl esters of the fatty acids are separated and measured using a Hewlett-Packard 5880 gas

chromatograph with a six foot column packed with 10% silar on chromosorb WAW 106/230. The carrier gas is helium (30ml/min). Oven temperature is programmed to rise from 165°C to 190°C at 2°C/min. Detector temperature is 220°C and injector temperature 200°C. Retention times and peak areas are automatically computed by Hewlett-Packard Level 4 integrator. Peaks are identified by comparison with standard fatty acid methyl esters.

PACKS

If it is not desired to have compositions comprising different active materials together, packs may be prepared comprising the materials presented for separate, or part joint and part separate use in the appropriate relative amounts, and such packs are within the purview of this invention. In particular the glucocortocoid may be for application to the skin but the EFA as an oral or other preparation to be used at the same time. Such preparation may be in a suitable pharmaceutical vehicle, as discussed in detail for example in Williams British Patent Specification No. 1 082 624, to which reference may be made, and in any case very well known generally for any particular kind of preparation. Thus, for example, tablets, capsules, ingestible liquid or powder preparations can be prepared as required. Injectable solutions of hydrolysed Oenothera oil may be prepared using albumin to solubilise the free acid. The amounts of EFA are such as to give daily dosages of 0.1 mg to 10 g preferably 30 mg to 1 g.

VETERINARY APPLICATIONS

It will be understood that where a disorder of a kind calling for treatment in animals arises, the invention whilst described primarily in terms of human medicine and treatment is equally applicable in the veterinary field.

FORMS AND SOURCES OF γ-LINOLENIC AND DIHOMO-γ-LINOLENIC ACIDS

Convenient physiologically functional derivatives of γ-linolenic acid and dihomo-γ-linolenic acid for use according to the invention include salts, amides, esters including glycerides and alkyl (e.g. C_1 to C_4) esters, and phospholipids.

If desired, pharmaceutical compositions may be produced for use in the invention by associating the natural or synthetic acids, as such or as derivatives, with an acceptable pharmaceutical vehicle. It is, however, at present convenient to incorporate at least the γ-linolenic acid into compositions in the form of an available oil having a high γ-linolenic acid content, hence references to "oil" herein.

At the present time known natural sources of oils having a high γ-linolenic acid content are few (there are no known natural sources of significant amounts of dihomo-γ-linolenic acid). One source of oils currently available is the seed of Evening Primrose species such as Oenothera biennis L. and Oenothera lamarckiana, the oil extract therefrom containing γ-linolenic acid (about 8%) and linoleic acid (about 72%) in the form of of their glycerides together with other glycerides (percentages

based on total fatty acids). Other sources of γ-linolenic acid are Borage species such as Borago officinalis which, though current yield per acre is low, provides a richer source of γ-linolenic acid than Oenothera oil. Recent studies on fungi which can be cultivated by fermentation promise a fungal oil source.

The seed oil extracts referred to above can be used as such or can for example if desired be fractionated to yield an oily composition containing the triglycerides of γ-linolenic and linoleic as the main fatty acid components, the γ-linolenic acid content being if desired a major proportion. Seed oil extracts appear to have a stabilising effect upon dihomo-γ-linolenic acid if present.

The Oenothera oil is extracted from the seeds by one of the conventional methods of extraction such as cold pressure, screw pressure after partially cooking the seed, or solvent extraction.

Fractionation of a typical sample of this oil in the form of methyl esters shows the relative proportions:

Palmitate	6.15
Stearate	1.6
Oleate	10.15
Linoleate	72.6
γ-Linolenate	8.9

As preservative, α-tocopherol may be added to the oil in a

concentration of 0.1%.

EXAMPLES

The following Examples are of ointments for use against psoriasis and against contact, atopic or seborrhoeic dermatitis applied one or more times daily.

In each of these Examples, the preparation is made up to 100% with a cream, ointment, lotion or other base suitable for topical application as standard in the art.

EXAMPLE 1

Hydrocortisone	1%
GLA	1%

EXAMPLE 2

Hydrocortisone	2%
EPA	1%

EXAMPLE 3

Hydrocortisone	1%
Columbinic acid	2%

EXAMPLE 4

Hydrocortisone	2%
GLA	1%
EPA	0.1%
Columbinic acid	1%

EXAMPLE 5

Hydrocortisone	1%
GLA	2%
EPA	0.5%

EXAMPLE 6

Hydrocortisone	2%
GLA	2%
Columbinic acid	1%

In the above formulations, hydrocortisone may be replaced by equivalent steroids, e.g. prednisolone 0.5%, triamcinolone 0.1%, betamethasone 0.1%.

A pack may comprise a topical ointment with such amounts of steroid, together with capsules of the Oenothera oil above containing 0.5 g oil extract = ca. 0.045 g γ-linolenic acid to be taken in the requisite amounts.

CLAIMS

1. A topical composition for skin treatment containing an anti-inflammatory glucocorticoid in combination with an essential fatty acid (EFA) of the n-6 or n-3 series or equivalent polyunsaturated fatty acid, as such or in the form of a physiologically acceptable derivative convertible in the body thereto.

2. A composition according to claim 1, wherein the fatty acids are selected from GLA, DGLA, the 22:4 and 22:5 n-6 EFAs, the 18:4. 20:4, 20:5, 22:5 and 22:6 n-3 EFAs and columbinic acid.

3. A composition according to claim 1 or 2 wherein the glucocortocoid is hydrocortisone, cortisone, betamethasone, dexamethasone, fluprednisolone, methylprednisolone, paramethasone, prednisone, prednisolone, triamcinolone, beclomethasone, clobetasol cloprednol, cortivazol, deoxycortone, desonide, desoxymethasone, diflucortolone, fluclorolone, fludrocortisone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortolone, fluoromethalone, fluperolone, fluprednidene, flurandrenolone, formocortal halcinonide, hydrocortamate, medrysone, methylprednisone, parameth-asone, prednisolamate and prednylidene.

4. A composition according to any preceding claim containing by weight, 0.01 to 30% fatty acid, 0.01 to 10% glucocorticoid in a topical application base.

5. A pack comprising a glucocortocoid and an EFA as set out

in claim 1, 2 or 3 presented for separate but simultaneous use.

6. A pack according to claim 5 wherein the glucocortocoid is present as a topical preparation comprising 0.01 to 10% glucocorticoid by weight and the EFA as an oral or other internally absorbable preparation to give 0.1mg to 10g EFA daily.

7. The use of a glucocortocoid and an EFA for the manufacture of a topical medicament as specified in claim 1, 2 3 or 4 or a pack as set out in claim 5 or 6 for treatment of inflammatory conditions of the skin.

0173478

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EUROPEAN SEARCH REPORT

Application number
EP 85 30 5552

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	US-A-4 305 936 (R.W. KLEIN) * Column 8, lines 4-11; claim 1 *	1-7	A 61 K 35/78 A 61 K 31/57 // (A 61 K 35/78 A 61 K 31:57) (A 61 K 31/57 A 61 K 31:23 A 61 K 31:20)
A	EP-A-0 003 407 (VERRONMAY LTD.) * Page 3, lines 11-25 *	1-7	
A	EP-A-0 085 579 (D.F. HORROBIN) * Page 6, lines 16-34 *	1-7	
D,A	GB-A-1 082 624 (CALMIC LTD.)	1-7	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	25-11-1985	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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